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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,579	11/02/2000	Brian M. Fendly	P1053R1D1	5667

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Genentech Inc
Wendy M Lee
1DNA Way
South San Francisco, CA 94080-4990

EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	8

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/705,579	FENDLY, BRIAN M.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-66* is/are pending in the application.

4a) Of the above claim(s) *43 and 45-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,44,55,56 and 59-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group II in Paper No. 6 is acknowledged.

2. Claims 57-58 are canceled without prejudice, claims 42-56 and 59-66 are pending. Claims 43, 45-54 are withdrawn from consideration as being drawn to a non-elected subject matter. Applicants amendment to claim 42 to recite subject matter encompassed by claims 57-58 is acknowledged, as a result, claims 42, 44, 55-56, 59-66 are examined on the merits.

3. This application contains claims 43, 45-54 are drawn to an invention nonelected without traverse in Paper No. 6. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

4. The Information Disclosure Statement filed 2/2/01 (paper no. 2) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. Claims 42, 44, 55-56, and 59-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 42, 59, 61, 63, and dependent claims thereof, in the recitation of "effective", it renders the claim vague and indefinite because the term is relative. One

of skill in the art would not be able to determine what amount would constitute an effective amount, as such the metes and bounds of the term cannot be determined.

7. Regarding claims 55-56, and 66 in the recitation of "cross-block", it renders the claims vague and indefinite because it is not clear as to whether the action of cross-blocking is due to binding to the same epitope or whether it is due to steric hindrance.

Claim Rejections - 35 USC § 112, 1st paragraph

8. Claims 42, 44, 55-56, and 59-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of in vitro treatment of tumor cell lines that over-express ErbB2 comprising the administration of anti-ErbB2 antibodies 4D5, 7C2, and 7F3, does not reasonably provide enablement for a method of in vivo treatment of tumors or cancers over-expressing ErbB2 with any anti-ErbB2 antibody and chemotherapeutics, wherein the antibody is able to cross-block. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond

that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claims of the instant invention are drawn to a method of treating cancer or tumors characterized by the over-expression or activation of ErbB2 comprising the administration of an anti-ErbB2 antibody and a chemotherapeutic agent or growth inhibitory agent, wherein the tumor is a colorectal tumor and the chemotherapeutic agent of growth inhibitory agent is of the vinca family.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the treatments of cancers with antibody therapy can often be challenging and unsuccessful. One such example Seaver S (Genetic Engineering News 1994 Aug; 14(14):10&21) teaches that despite the promising results of many monoclonal antibodies in vitro, their transition to in vivo therapy has met with some problems. Such problems include bio-availability, localization to the tumor, clearance of antibody, ability

for the antibody to elicit correct immune response and development to antibodies to the antibody administered.

The amount of direction or guidance present and the presence or absence of working examples: The working examples of the instant invention are drawn to methods of in vitro cell death or induction of apoptosis caused by either 4D5, 7C2, or 7F3. No where in the specification does it teach to one of skill in the art how to use any other antibody for the treatment of cancer or tumors in an *in vivo* capacity. Based on the teachings of unpredictability regarding *in vivo* therapy which are taught in the prior art, persons skilled in the art would not associate *in vitro* results with *in vivo* therapeutic efficacy. Applicant's specification fails to contain sufficient disclosure to overcome the teachings of unpredictability which are found in the art. *Ex parte Balzarini* 21USPQ2d 1892 (BdPatAppl&Int. 1991). Further, the combination of the antibody with chemotherapeutics has not been disclosed. There are many factors which would cause one of skill in the art to experiment. Such factors include the dosage of chemotherapeutics and antibody needed, the side effects associated with the combination of chemotherapeutics, the clearance rates of the antibody, and whether the combination of antibody and chemotherapeutics is even effective.

In addition, the specification has specifically taught three specific antibodies, namely, 4D5, 7C2, and 7F3. The epitope recognized by 4D5 is located in the extracellular membrane proximal region of the ErbB2 receptor, while the epitope recognized by 7C2 and 7F3 are located in extracellular domain 1 of the ErbB2 receptor. No where in the specification does it teach any antibody that is capable of "cross-

blocking" either 4D5, 7C2, or 7F3. The lack of such disclosure would cause one of skill in the art to experiment, namely make an antibody and then screen the antibody for the effects encompassed by the claims. And as taught by Seaver S, the screening of antibodies, although possible, is not an easy task, of which "a minimum of 1000 clones nee to be screened to find 1-2 monoclonal antibodies".

The breadth of the claims and the quantity of experimentation needed: Given the lack of an enabling disclosure which teaches a method of in vivo tumor or cancer treatment comprising the administration of an anti-ErbB2 antibody and chemotherapeutics, of which the antibodies encompassed and the combination of antibody and chemotherapeutics has not been adequately disclosed, and absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily

published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 42, 44, and 59-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Hudziak *et al* (US Pat No. 5,720,954, IDS). Claims are drawn to a method of treating a cancer or tumor that overexpresses ErbB2, comprising the administration of an anti-ErbB2 antibody and a chemotherapeutic agent, wherein the tumor or cancer is a colorectal tumor, wherein the chemotherapeutic agent or growth inhibitory agent is able to kill or inhibit tumor growth, and is selected from the vinca family. Hudziak *et al* teach a method of treating a patient having a carcinoma that over-expresses HER2 (also known as erbB2, c-erbB2 or p185) wherein the carcinoma is any carcinoma over-expressing HER2, comprising the administration of an anti-HER2 antibody and a chemotherapeutic agent, wherein the chemotherapeutic agent is selected from the vinca family.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Baselga *et al* (Ann. Oncol. 1994;5(Suppl 5):A010, IDS) teach a method of treating tumors or cancer comprising the administration of an anti-HER2 antibody (4D5) in combination with chemotherapeutics.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
November 15, 2002

ALI R. SALIMI
PRIMARY EXAMINER